

ADT US 5219740 A US 1987-14579 19870213

PRAI US 1987-14579 19870213

IC ICM C12N005-10

ICS C12N015-86

AB US 5219740 A UPAB: 19931116

A novel process (I) of gene transfer into diploid **fibroblasts** in vitro comprises genetically modifying diploid **fibroblasts** explanted from a mammalian subject by a process consisting of introducing into the **fibroblasts** a retroviral construct comprising a first nucleotide sequence encoding a first expresssion prod., a viral long terminal repeat (LTR) and a promoter sequence upstream of the first nucleic acid sequence, and a viral LTR and a polyadenylation sequence downstream of the first nucleotide sequence, where the retroviral construct lacks one or more of the gag, pol and env sequence required for retroviral replication, by contacting the **fibroblasts** with the retroviral construct in a virus-containing medium having a viral titer of at least 10 power 5 cfu/ml on NIH 3T3 **fibroblasts** to produce a population of **fibroblasts** at least 10% of which express the first expression prod..

USE/ADVANTAGE - The process provides for mammalian gene therapy. The explanted **fibroblasts** are genetically modified to introduce gene of therapeutic importance so as to permit and facilitate the expression of the introduced gene(s) following implantation of the modified **fibroblasts** into the patient. The recipient of the modified **fibroblasts** will typically be deficient in the therapeutic prod., e.g. an enzyme, hormone or precursor, e.g. adenosine deaminase, purine nucleoside phosphorylase and blood clotting factor VIII and IX.

Dwg.0/5

FS CPI

FA AB

MC CPI: B04-B04A3; C04-B04A3; B11-C09; C11-C09; D05-H12

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(FILE 'HOME' ENTERED AT 11:20:05 ON 24 MAY 2005)

SET COST OFF

FILE 'BIOSIS' ENTERED AT 11:20:19 ON 24 MAY 2005

	E SIMMONS P/AU
L1	282 S E3-E14,E16-E19
	E GRONTHOS S/AU
L2	35 S E3,E4
	E ZANNETTINO A/AU
L3	50 S E3-E6
	E ZANETINO A/AU
	E ZANNETTINO A/AU
L4	3 S E3-E5
	E ZANETTINO A/AU
L5	322 S L1-L4
L6	18 S L5 AND ?MESENCHYM?
L7	26 S L5 AND CFU
L8	10 S L5 AND CFU F
L9	7 S L5 AND CFU(L) FIBROBLAST?
L10	20 S L5 AND COLON? FORM? UNIT?
L11	9 S L10 AND (F OR FIBROBLAST?)
L12	28 S L6,L8,L9,L11
L13	17 S L6-L11 NOT L12
L14	232 S L5 AND PY<=2000
L15	11 S L5 AND P/DT

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                SEL DN AN 1 4 8
L16             3 S L15 AND E1-E6
L17             10 S L14 AND L12
L18             13 S L16,L17
L19             18 S L12 NOT L18
L20             99 S L14 AND 00520/CC
L21             116 S L14 AND (CONGRESS? OR CONFERENC? OR POSTER? OR SYMPOS? OR MEE
L22             17 S L21 NOT L20
L23             2 S L22 AND CONFERENCE?/DT
L24             101 S L20,L23
L25             8 S L24 AND L6-L13,L17-L19
L26             7 S L25 NOT LTC/TI
L27             15 S L18,L26
L28             14 S L27 NOT CFU S
L29             14 S L28 AND L1-L28

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FILE 'BIOSIS' ENTERED AT 11:31:32 ON 24 MAY 2005

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L30             325 S CFU F OR COLON? FORM? UNIT? F
L31             110 S CFU FIBROBLAST? OR COLON? FORM? UNIT? FIBROBLAST?
L32             277 S L30,L31 AND PY<=2000
L33             414 S COLON? FORM? UNIT?(L) FIBROBLAST?
L34             317 S L33 AND PY<=2000
L35             408 S L33,L34 NOT L29
L36             39 S L35 AND ?MESENCHYM?
L37             142 S L35 AND (LFA 3 OR THY 1 OR STRO1 OR STRO2 OR STRO() (1 OR 2) O
L38             3 S L35 AND PEROXISOM? PROLIFERAT? ACTIVAT? RECEPTOR?
L39             8 S L35 AND (CD ANTIGEN OR CD49# OR CD29 OR CD18 OR CD61 OR 6 19
L40             32 S L35 AND ?MARKER?
L41             28 S L35 AND ?ANTIGEN?
L42             166 S L37-L41
L43             32 S L36 AND L42
L44             7 S L36 NOT L43
L45             198 S L35 AND STROMA?
L46             48 S L45 AND L36,L40,L41
L47             23 S L46 NOT L43,L44
                SEL DN AN 2 6 9 10 11 13 20 22 23
L48             9 S L47 AND E7-E27
                SEL DN AN L43 3-5 8 9 13 30 31
L49             24 S L43 NOT E28-E43
L50             33 S L48,L49 AND L1-L49
L51             7 S L50 AND ENRICH?
L52             21 S L50 AND ?CULTUR?
L53             21 S L51,L52
L54             12 S L50 NOT L53
L55             33 S L53,L54

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FILE 'WPIX' ENTERED AT 11:47:30 ON 24 MAY 2005

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L56             12 S L30/BIX OR L31/BIX OR L33/BIX OR (CFU (L) FIBROBLAST?)/BIX
L57             7 S L56 AND ?MESENCHYM?/BIX
L58             8 S L56 AND C12N/IPC
L59             11 S L57,L58
L60             12 S L56-L59
L61             1 S L60 AND (SIMMONS P? OR GRONTHOS S? OR ZANNETTINO ? OR ZANETTI
L62             1 S L60 AND MEDVET?/PA
L63             1 S L61,L62
L64             11 S L60 NOT L63

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FILE 'WPIX' ENTERED AT 11:54:28 ON 24 MAY 2005

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of)

IT Antigens
RL: PROC (Process)
(VLA-1, of bone marrow of human, cellular localization of)

IT Antigens
RL: PROC (Process)
(VLA-2, of bone marrow of human, cellular localization of)

IT Antigens
RL: PROC (Process)
(VLA-4, of bone marrow of human, cellular localization of)

IT Antigens
RL: PROC (Process)
(VLA-6, of bone marrow of human, cellular localization of)

IT Bone marrow, composition
(endothelium, integrins of, of human)

IT **Hematopoietic precursor cell**
(erythroid, integrins of, in humans)

IT Glycoproteins, specific or class
RL: BIOL (Biological study)
(integrins, α β 3, α -subunit, of
bone marrow of human, cellular localization of)

IT **Hematopoietic precursor cell**
(macrophage-monocyte-forming, integrins of, in humans)

IT **Hematopoietic precursor cell**
(myeloid, integrins of, in humans)

IT Antigens
RL: PROC (Process)
(p150,95, of bone marrow of human, cellular localization of)

IT Bone marrow, composition
(stroma, **fibroblast colony-forming unit**, integrins of, in humans)

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(FILE 'HOME' ENTERED AT 09:08:53 ON 24 MAY 2005)
SET COST OFF

FILE 'HCAPLUS' ENTERED AT 09:09:05 ON 24 MAY 2005

E SIMMONS P/AU

L1 141 S E3-E8,E12-E19
E ZANNETTINO A/AU

L2 42 S E3-E6
E GRONTHOS S/AU

L3 30 S E3,E4
E ZANNET /AU

L4 2 S E6,E7
E ZANET /AU

L5 1 S E205
E MDEVET/PA,CS
E MEDVET/PA,CS

L6 46 S E3-E12

L7 216 S L1-L6

L8 2 S (WO2000-AU822 OR AU99-1477)/AP,PRN

L9 2 S L7 AND L8

L10 19 S L7 AND CFU

L11 6 S L7 AND COLON? (L) FORM? (L) UNIT? (L) FIBROBLAST?

L12 6 S L10 AND F

L13 6 S L10 AND FIBROBLAST?

L14 10 S L7 AND ?MESENCHYM?

L15 16 S L11-L14
 L16 68 S L7 AND P/DT NOT L15
 L17 6 S L15 AND (PY<=2000 OR PRY<=2000 OR AY<=2000)
 L18 10 S L15 NOT L17
 L19 752 S ?MESENCHYM? (L) ?PRECURS?
 L20 710 S ?MESENCHYM? (L) ?PRECURS? (L) CELL
 L21 733 S ?MESENCHYM? (L) ?PROGENIT? (L) CELL
 L22 752 S ?MESENCHYM? (L) ?PROGENIT?
 L23 1899 S ?MESENCHYM? (L) STEM (L) CELL
 L24 510 S ?MESENCHYM? (L) (?HEMATOPOI? OR ?HAEMATOPAI? OR ?HEMAPOI? OR
 E MESENCHYM/CT
 E E8+ALL
 L25 3137 S E3+NT
 L26 977 S L25 AND L19-L24
 E STEM CELL/CT
 E E3+ALL
 L27 568 S E3,E2+NT (L) ?MESENCHYM?
 E HEMATOPOIETIC/CT
 E E21+ALL
 L28 76 S E11,E10 (L) ?MESENCHYM?
 L29 2948 S L19-L24,L26-L28
 L30 10 S L29 AND L7
 L31 2 S L30 AND L17
 L32 10 S L30 AND L15
 L33 6 S L17,L31
 L34 10 S L15,L32 NOT L33

FILE 'HCAPLUS' ENTERED AT 09:44:48 ON 24 MAY 2005

E FIBROBLAST/CT
 E E3+ALL
 L35 9 S E4,E3 (L) COLON? FORM? UNIT
 L36 3 S E4,E3 (L) CFU
 L37 10 S L35,L36
 L38 242 S FIBROBLAST? (L) CFU
 L39 230 S FIBROBLAST? (L) COLON? FORM? UNIT
 L40 329 S L37-L39
 L41 235 S L40 AND (PY<=2000 OR PRY<=2000 OR AY<=2000)
 L42 12 S L41 AND ?MESENCHYM?
 L43 160 S L41 AND (?PRECURS? OR ?PROGENIT? OR STEM CELL)
 L44 149 S L41 AND (?HEMATOPOI? OR ?HAEMATOPAI? OR ?HEMAPOI? OR ?HAEMAPO
 L45 184 S L42-L44
 L46 20 S L45 AND (STRO1 OR STRO2 OR STRO() (1 OR 2) OR VCAM OR ICAM OR
 L47 1 S L45 AND (CD ANTIGEN OR CELL ADHESION MOLECULE OR INTERCELL? A
 L48 1 S L45 AND (PPAR? OR PPAR GAMMA 2)
 L49 33 S L46-L48,L42
 L50 30 S L49 NOT L30-L34
 L51 1 S L45 AND PEROXISOM? PROLIFERAT? ACTIVAT? RECEPTOR?
 L52 5 S L37 AND L41 NOT L30-L34
 L53 34 S L50,L51,L52
 L54 34 S L53 AND L1-L53
 L55 34 S L54 AND (CFU OR COLON? FORM? UNIT?)
 L56 25 S L55 AND (COLON? FORM? UNIT?)
 L57 9 S L55 NOT L56
 SEL DN AN 2 9
 L58 2 S L57 AND E1-E6
 L59 10 S L56 AND L42
 L60 12 S L58,L59
 L61 15 S L56 NOT L60
 SEL DN AN 1 6 11 13
 L62 4 S L61 AND E7-E18